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Tetrasomy 5p Mosaicism Due to an Extra i(5p) in a Severely Affected Girl

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We present a case of mosaic 5p tetrasomy. The mosaicism 46,XX/47,XX,+i(5p) was found at different ratios in blood lymphocytes, skin fibroblasts, and chondrocytes. The origin of the extra isochromosome was confirmed by FISH. The clinical picture corresponds to that described in trisomy 5p patients, although it was more severe than the two previously reported cases of mosaic 5p tetrasomy. No correlation between clinical severity and proportion of tetrasomic cells in blood or fibroblasts was found in these cases. Am. J. Med. Genet. 68:481–484, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: isochromosome 5p; mosaicism; FISH; trisomy 5p syndrome; tetrasomy 5p

INTRODUCTION

Isochromosome 5p was reported in four cases with only one normal chromosome 5, leading to trisomy 5p [Cordero et al., 1977; Leshot and Lim, 1979; Orye et al., 1983; Fujita et al., 1994]. The clinical picture of these patients is consistent with the pattern delineated in cases with complete and partial trisomy 5p affecting at least band 5p13 (Lorda-Sanchez et al., 1997). This includes: generalized hypotonia, macrocephaly, facial anomalies, short neck, club feet, feeding and respiratory difficulties, and anomalies of the central nervous system with dilated cerebral ventricles and hydrocephaly as main complication.

An isochromosome 5p was also found in two recently published cases with tetrasomy 5p mosaicism [Stanley et al., 1993; Sijmons et al., 1993]. The clinical findings observed in the case reported by Sijmons et al. [1993] are consistent with the above described clinical pattern resulting from cases of trisomy 5p, whereas the case published by Stanley et al. [1993] showed only mild phenotypic findings. The differences between the two tetrasomy patients were presumed to be due to percentage of i(5p) and tissue distribution of the mosaicism [Sijmons et al., 1993].

Here we present the third case of tetrasomy 5p mosaicism with a clinical picture similar to that of trisomy 5p. The infant was ascertained through the Spanish Collaborative Study of Congenital Malformations (ECEMC).

CLINICAL REPORT

The proposita was born at term after an uneventful pregnancy. She was the fifth child of nonconsanguineous and healthy parents, a 31-year-old mother and a 30-year-old father. One child was born prematurely at the 28th week without apparent malformations and died after 40 days of life. The remaining 3 children were healthy. The father has a nephew with hydrocephaly and psychomotor retardation of unknown cause. A brother of the mother has Down syndrome.

At birth, the proposita's weight was 3,040 g (50th centile), length 46 cm (10–25th centile), and head circumference (OFC) 35.5 cm (90th centile). Clinical examination showed a coarse, flat face with short nose and anteverted nares, midface hypoplasia, full cheeks, long philtrum, micrognathia, and malformed and posteriorly angulated ears with bilateral preauricular pits. The neck was short with redundant skin folds. The hands showed long fingers and mild fifth finger clinodactyly. Feet were clubbed, with short and proximally implanted hallux and overriding toes. The child also had a bell-shape thorax and extreme hypoplasia of abdominal muscles (Fig. 1).

Some indirect signs of pulmonar hypertension, but no congenital heart defect, were observed at echocardiography. Evaluation of the relative macrocephaly by cerebral ultrasound showed a tetraventricular hydrocephaly with a right localized intraventricular hemorrhage. Cerebral CT scan confirmed the latter findings

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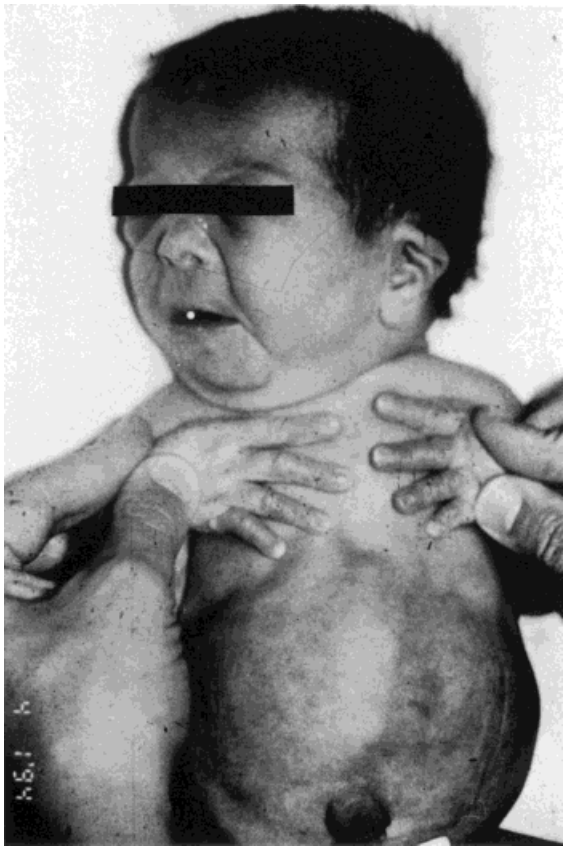

Fig. 1. Patient at birth.

and showed additionally a lipoma in the anterior portion of the corpus callosum and a large cisterna magna with hypoplastic right cerebellar hemisphere. It was interpreted as a Dandy-Walker anomaly. The progressive hydrocephaly required drainage at age 25 days.

The infant stayed hospitalized due to feeding difficulties with failure to thrive, recurrent infections, and cardiorespiratory distress. The pulmonary hypertension persisted with cyanosis and signs of cardiac insufficiency. At the age of 5.5 months, her weight was 5,850 g (<3rd centile), length 58 cm (<3rd centile), and OFC 43cm (50th centile). She died at 6 months due to cardiorespiratory failure. Consent for the autopsy was denied by the parents.

CYTOGENETIC STUDIES

Chromosome analysis was performed on blood lymphocytes, skin fibroblasts, and chondrocytes. Of 83 lymphocytes analyzed, 82 showed a normal female karyotype, and only one cell showed a marker (46XX/47,XX, +mar). Skin tissue and cartilage were obtained after death and cultured according to the standard protocols in our lab [Urioste, 1993]. Cell subcultures of both tissues were stored at −84°C using glycerol as cryoprotective agent [Verma and Babu, 1989].

Among the 63 metaphases from the skin fibroblasts, 23 (37%) had the marker chromosome. The same marker was found in 50% of the 30 metaphases analyzed from

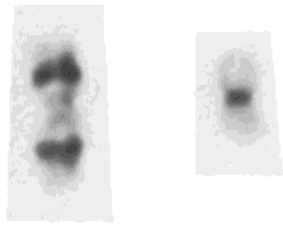

Fig. 2. Partial GTG and CBG banded karyotype showing the marker chromosome.

cultured chondrocytes. C-banding showed an apparently monocentric isochromosome. The marker was tentatively interpreted as an isochromosome 5p (Fig. 2).

FISH analysis with a library for chromosome 5 (COATOSOME total chromosome 5; ONCOR) was performed according to manufacturer's instructions on chromosome preparations obtained from thawed cultured cartilage cells, after 6 months of storage at −84°C. The complete fluorescence of the two normal chromosomes 5, as well as the marker chromosome, supported the interpretation of the extra material as derived from chromosome 5 (Fig. 3).

DISCUSSION

Clinical comparisons between tri- and tetrasomies for the same segment are frequently difficult due to the presence of mosaicism [Schinzel, 1993]. To our knowledge, there is no report of nonmosaic 5p tetrasomy and there are only two previous reports on mosaic cases. The present case, as well as the patient reported by Sijmons et al. [1993], shared the clinical picture of com-

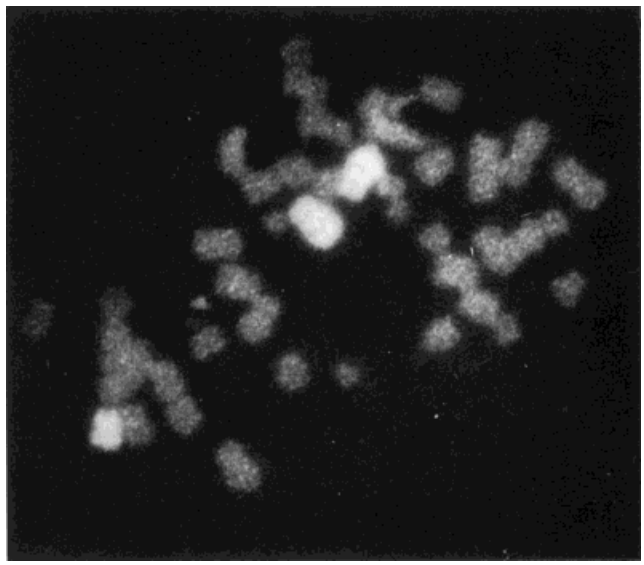

Fig. 3. A partial metaphase cell from the patient hybridized in situ with a library for chromosome 5, showing a complete fluorescence of both normal chromosome 5 and the marker chromosome.

TABLE I. Comparison of the Present Case With Previously Reported Cases With Mosaic Tetrasomy 5p and Complete Trisomy 5p Due to i(5p)

	Mosaic tetrasomy 5p due to i(5p)			Complete trisomy 5p due to translocaton + i(5p)		
	Stanley et al., 1993	Sijmons et al., 1993	Present case	Leshot and Lim, 1979	Orye et al., 1983	Fujita et al., 1994
Sex	Female	Male	Female	Female	Male	Male
Gestational age	40 w	34 w	39 w	42 w	At term	36 w
Birthweight (g)	2,670	2,550	3,040	2,990	3,050	2,600
Birthlength (cm)			46	50	51	
OFC at birth (cm)			36.5	36	37.5	37.5
Hypotonia	x	x	x	x	x	x
Ventriculomegaly		x	x	x		x
Seizures/abnormal EEG	x	x	x	x		x
Psychomotor retardation	x	x	x			x
Macrocephaly		x	x	x	x	x
Dolichocephaly		x		x	x	
Enlarged ant. fontanelle					x	
Prominent sutures					x	
Depressed supraorbital ridges			x		x	
Epicanthal folds	x			x		x
Upslaning palpebral fissures	x	x		x	x	x
Hypertelorism		x		x	x	x
Broad/deep nasal bridge		x		x	x	x
Short nose			x	x	x	x
Anteverted nasal tip	x		x			x
Midface hypoplasia			x	x	x	x
Long philtrum	x		x		x	x
High arched palate	x					
Microretrognathia		x	x	x	x	x
Low set “dysplastic” ears		x	x	x	x	x
Preauricular pits		x	x			
Short neck			x	x	x	x
Redundant skin folds			x	x	x	x
Club feet			x	x	x	x
Proximally implanted—short first toe			x	x	x	
Overlapping toes		x	x			
Proximally implanted thumbs				x	x	
Fifth finger clinodactyly	x		x			
Hyperpigmentation	x					
Abdominal muscles hypoplasia/umbilical hernia			x	x		
Holosystolic murmur			x	x	x	
Low pitched /weak cry			x	x		
Respiratory difficulties		x	x	x		x
Recurrent resp. infections			x	x		x
Failure to thrive			x	x	x	
Early death			6 mos		52 days	38 weeks
Proportion of cells with the i(5p) (no. of cells analyzed)						
in lymphocytes	0% (25)	10% (31)	1.2% (83)	100%	100%	100%
in skin fibroblasts	60% (30)	85% (28)	37% (37)			
in chorion villus cytotrophoblasts		0.5% (201)				
in chondrocytes			50% (30)			
Maternal age	29	40	31	31	28	26
Paternal age	29	40	30	30	26	26

plete 5p trisomy (Table I). A milder phenotype with only some components of complete 5p trisomy was observed in the patient reported by Stanley et al. [1993].

The clinical differences between tetrasomy patients were presumed to be due to tissue distribution of the mosaicism and percentage of cells with i(5p) [Sijmons et al., 1993]. Tetrasomy 5p, like tetrasomy 12p, is usually demonstrated in cytogenetic studies of skin fibroblasts and might not be detectable in pheripheral blood lymphocytes. The present case showed the most severe clinical picture and the lowest proportion of tetrasomic cells in fibroblasts (Table I). This apparent lack of correlation between clinical severity and proportion of tetrasomic cells in lymphocytes and fibroblasts also has been observed in mosaic tetrasomy 12p [Schinzel, 1991]. Using in situ hybridization in peripheral blood lymphocytes, Thornberg-Reeser and Werger [1992] observed a higher proportion of i(12p) in interphase nu-

clei than in metaphase, suggesting that the low degree of mosaicism observed in routine metaphase analysis of blood samples might be biased by an in vitro selective division of normal cells. Therefore, the frequency with which the isochromosome is observed at mitosis in different tissues may not necessarily reflect the actual distribution of the abnormal cell line. Further studies to determine the percentage of mosaicism in other tissues, taking into account the possible in vitro selective growth of a given cell-line, are necessary to clarify this correlation.

The variable mosaic ratios of tetrasomy 5p in the different analyzed tissues may lead to a false negative cytogenetic diagnosis, if only blood samples [Stanley et al., 1993] or chorion cytotrophoblasts are studied [Sijmons et al., 1993]. Additionally, some cytogenetic similarities between i(5p) and i(12p) make a misdiagnosis possible in patients with clinical findings typical of both tetrasomies, and such as pigmentary abnormalities [Stanley et al., 1993]. Taking the possible failure of detection and misdiagnosis into account, the occurrence of mosaic 5p tetrasomy may actually be more frequent than is reported. The diagnosis of further cases may be improved by cytogenetic analysis of skin fibroblasts in patients with manifestations consistent with 5p tri- and tetrasomies and by more routine use of FISH to test the mosaicism in pheripheral blood interphase cells and also to determine the origin of marker chromosomes.

The occurrence of partial tetrasomies due to an extra isochromosome could be explained by different meiotic and mitotic mechanisms. Sijmons et al. [1993] proposed a postzygotic partial endoreduplication event after incorrect ligation as the most attractive model to explain their case. For Van Dyke [1988], the maternal age effect, although it is not demonstrable in tetrasomy 5p due to the few reported cases (Table I), but is observed in Pallister-Killian i(12p) syndrome and other partial tetrasomies, supports a meiotic rather than a postzygotic origin of the extra isochromosome. The use of highly informative molecular polymorphisms to determine parental origin and iso- versus heteromorphism of the isochromosomes, as has been done in inv dup (15) supernumerary marker chromosomes [Robinson et al., 1993], should be helpful in further assessment of the mechanisms of extra isochromosome formation.

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